

Remarks

Reconsideration of this Application is respectfully requested. Based on the foregoing amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Amendments to the Specification

Applicants have amended paragraphs 41-43, 49, 50-51, 53-55, 58-62, 80, 140 and 228. Paragraphs 41-43, 49, 50-51, 53-55 and 58-62 correspond to the figure legends of figures 4-6, 12, 13-14, 16-18 and 21-25.

Paragraphs 41-43, 50-51, 53, 140 and 228 were amended as requested by the Examiner in paragraph 6 at page 3 of the Office Action, and these amendments will be addressed in sections VI and VIII of this Amendment and Response. Paragraphs 49, 54-55 and 58-62 were amended to facilitate consistency between the figures and their corresponding figure legends.

Paragraph 49 was amended to describe the content of each panel of the corresponding figure. Support for the amendment to paragraph 49 can be found on page 16, paragraph 49 and page 98, paragraph 271 of the specification.

Paragraph 54 was amended to define the descriptive labels shown in the corresponding figure. Support for the amendment to paragraph 54 can be found on page 17, paragraph 54 and page 100, paragraph 280 of the specification.

Paragraph 55 was amended to define the descriptive labels shown in the corresponding figure. Support for the amendment to paragraph 55 can be found on page 17, paragraph 55 and pages 100-101, paragraph 282 of the specification.

Paragraph 58 was amended to define the alphabetic labels shown in the corresponding figure. Support for the amendment to paragraph 58 can be found on page 18, paragraph 58 and page 101, paragraph 284 of the specification.

Paragraph 59 was amended to define each treatment shown in the corresponding figure. Support for the amendment to paragraph 59 can be found on page 18, paragraph 59 and page 103, paragraph 287 of the specification.

Paragraph 60 was amended to define each treatment shown in the corresponding figure. Support for the amendment to paragraph 60 can be found on pages 18-19, paragraph 60 and pages 103-104, paragraph 288 of the specification.

Paragraph 61 was amended to define the alphabetic labels shown in the corresponding figure. Support for the amendment to paragraph 61 can be found on page 19, paragraph 61 and page 104, paragraph 289 of the specification.

Paragraph 62 was amended to define the alphabetic designations shown in the corresponding figure. Support for the amendment to paragraph 62 can be found on page 19, paragraph 62 and page 106, paragraph 295 of the specification.

Paragraph 80 was amended to remove the embedded hyperlink objected to by the Examiner at page 3 of the Office Action.

II. Status of the Claims

Upon entry of the foregoing amendment, 236 claims are pending in the application, with claims 95 and 213 being the independent claims. Claims 1-94 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein.

New claims 95-330 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

III. Support for the New Claims

Support for new claims 95 and 213 may be found throughout the specification, *inter alia*, at pages 5-6, paragraphs 19-21, pages 38-39, paragraph 113, pages 45-46, paragraph 132, page 57, paragraph 165 and in claims 1 and 5 as filed.

Support for new claims 96 and 214 may be found throughout the specification, *inter alia*, at pages 39-40, paragraphs 116-117 and in claim 2 as filed.

Support for new claims 97, 110, 123, 136, 149, 162, 175, 188, 201, 215, 228, 241, 254, 267, 280, 293, 306 and 319 may be found throughout the specification, *inter alia*, at page 59, paragraph 171 and in claim 6 as filed.

Support for new claims 98, 111, 124, 137, 150, 163, 176, 189, 202, 216, 229, 242, 255, 268, 281, 294, 307 and 320 may be found throughout the specification, *inter alia*, at pages 57-58, paragraph 168 and in claim 7 as filed.

Support for new claims 99, 112, 125, 138, 151, 164, 177, 190, 203, 217, 230, 243, 256, 269, 282, 295, 308 and 321 may be found throughout the specification, *inter alia*, at page 50, paragraph 146.

Support for new claims 100, 113, 126, 139, 152, 165, 178, 191, 204, 218, 231, 244, 257, 270, 283, 296, 309 and 322 may be found throughout the specification, *inter alia*, at page 50, paragraph 146 and in claim 8 as filed.

Support for new claims 101, 114, 127, 140, 153, 166, 179, 192, 205, 219, 232, 245, 258, 271, 284, 297, 210 and 323 may be found throughout the specification, *inter alia*, at page 51, paragraph 148 and in claim 9 as filed.

Support for new claims 102, 115, 128, 141, 154, 167, 180, 193, 206, 220, 233, 246, 259, 272, 285, 298, 311 and 324 may be found throughout the specification, *inter alia*, at pages 50-52 , paragraphs 147-150 and in claim 10 as filed.

Support for new claims 103, 116, 129, 142, 155, 168, 181, 194, 207, 221, 234, 247, 260, 273, 286, 299, 312 and 325 may be found throughout the specification, *inter alia*, at page 46-50, paragraphs 133-145 and in claim 11 as filed.

Support for new claims 104, 107, 117, 120, 130, 133, 143, 146, 156, 159, 169, 172, 182, 185, 195, 198, 208, 211, 222, 225, 235, 238, 248, 251, 261, 264, 274, 277, 287, 290, 300, 303, 313, 316, 326 and 329 may be found throughout the specification, *inter alia*, at page 46, paragraph 133.

Support for new claims 105, 108, 118, 121, 131, 134, 144, 147, 157, 160, 170, 173, 183, 186, 196, 199, 209, 212, 223, 226, 236, 239, 249, 252, 262, 265, 275, 278, 288, 291, 301, 304, 314, 317, 327 and 330 may be found throughout the specification, *inter alia*, at page 46, paragraph 133.

Support for new claims 106, 119, 132, 145, 158, 171, 184, 197, 210, 224, 237, 250, 263, 276, 289, 302, 315 and 328 may be found throughout the specification, *inter alia*, at pages 46-50, paragraphs 133-145 and in claim 12 as filed.

Support for new claims 109 and 227 may be found throughout the specification, *inter alia*, at page 40, paragraph 118 and in claim 3 as filed.

Support for new claims 122 and 240 may be found throughout the specification, *inter alia*, at page 40-41, paragraph 119 and in claim 4 as filed.

Support for new claims 135 and 253 may be found throughout the specification, *inter alia*, at page 41, paragraph 120.

Support for new claims 148 and 266 may be found throughout the specification, *inter alia*, at pages 41-42, paragraphs 121-122.

Support for new claims 161 and 279 may be found throughout the specification, *inter alia*, at page 42, paragraph 123.

Support for new claims 174 and 292 may be found throughout the specification, *inter alia*, at page 103, paragraphs 286-287.

Support for new claims 187 and 305 may be found throughout the specification, *inter alia*, at page 42, paragraph 124.

Support for new claims 200 and 318 may be found throughout the specification, *inter alia*, at page 42, paragraph 124.

IV. The Declaration of Xiaoning Bi and Gary Lynch

The accompanying declaration of Xiaoning Bi and Gary Lynch has been executed only by Gary Lynch. Applicants were unable to obtain Dr. Bi's signature prior to the date of filing this Amendment and Reply. Applicants will file a copy of the declaration executed by Dr. Bi in a Supplemental Reply as soon as that declaration is received.

V. Description of the Invention

The present invention provides a model for studying the development of, and/or pathologies associated with neurodegenerative diseases, and agents that can alter such

development and/or pathologies. The model of the invention is especially useful as an Alzheimer's disease model and also recreates many of the specific pathologies associated with related neurodegenerative disorders. The model of the invention provides brain cells and a method for increasing neurodegenerative disease characteristics in such cells, especially, induction of neurofibrillary tangles and/or phosphorylated tau and/or tau fragments and/or the production and/or release of cytokines and/or microglia reactions and/or activations and/or inflammation and/or conversion of p35 to p25 and/or the levels and activities of protein kinases by selectively increasing the concentration of cathepsin D to an effective level, and/or by lowering the concentration of cholesterol in such cells. The model also provides a method of reversing such effects, by inhibiting cysteine protease and mitogen-activated kinase activity, and especially, by inhibiting calpain, and/or MAP kinases.

VI. Objections to the Specification

At page 2, paragraph 6 of the Office Action, the Examiner objected to the undefined term "AT8-ir." Applicants have amended paragraph 41 of the specification to define the term "AT8-ir."

At page 2, paragraph 6 of the Office Action, the Examiner requested that superscript be used throughout the specification for mutation designations for transgenic mice. Applicants have amended paragraphs 42, 140 and 228 of the specification to correct this informality.

At page 2, paragraph 7, the Examiner objects to the specification because of an embedded hyperlink in the text of the specification and requests that the hyperlink be

deleted. Applicants respectfully traverse the objection. However, in the interest of advancing prosecution, Applicants have deleted the hyperlink.

VII. Objection to the Abstract

At page 2, paragraph 5 of the Office Action, the Examiner objects on the basis that the application does not contain an abstract of the disclosure as required by 37 C.F.R. § 1.72. Applicants respectfully traverse the objection.

Applicants respectfully submit that an abstract of the disclosure was filed with the application. This abstract appears in the published application, therefore, the abstract was properly filed with the application. Copies of the abstract, the face page of the published application and a copy of the postcard indicating that the application was properly filed are provided with this Amendment and Response for the Examiner's review.

VIII. Objections to the Drawings

At page 3 of the Office Action, the Examiner has objected to Figures 6 and 10-16 for failing to designate portions of the drawings using alphanumeric labels, rather than the terms "left" and "right."

Applicants have amended Figures 6, 12 and 14 to label portions of the figures with alphabetic designations. Applicants respectfully submit that Figures 10, 11, 13 and 16 do not require amendment because they contain descriptive labels that match the descriptions in their corresponding figure legends. Figure 15 has been amended to label all lanes as described in its corresponding figure legend.

Applicants have also amended Figure 21 to label portions of the figure with alphabetic designations, and Applicants have amended Figures 17, 20, 22-23 and 26-27 to label lanes as described in their corresponding figure legends.

IX. Rejections under 35 U.S.C. § 112

In paragraph 8 at page 3 of the Office Action, the Examiner has rejected claims 1-12 under 35 U.S.C. § 112, first paragraph contending that the specification is not enabling for all neurodegenerative diseases, use of animal models other than mice, or the situations to create the conditions under which the method of the invention is carried out other than the claimed lysosomal inhibitors.

Applicants respectfully traverse the rejection. However, in order to expedite the allowance of the present application, Applicants have submitted new claims that refer the screening method to substances that affect characteristics of Alzheimer's Disease and related neurodegenerative disorders. The "related neurodegenerative disorders" are defined by the characteristics that they share with Alzheimer's Disease. Any related neurodegenerative disorders that share, with Alzheimer's Disease, the appearance of one or more of the characteristics in D(1)-D(9) of claims 95 and 213 can be assayed for in the model of the present invention. The new claims also refer to screening of rodent (rat and mouse) tissue and refer to those conditions caused by disruption of lysosomal activity.

The new claims effectively moot the Examiner's section 112, first paragraph rejection. Applicants, therefore, respectfully request reconsideration and withdrawal of this rejection.

In paragraph 17 at page 7 of the Office Action, the Examiner has also rejected claims 1-12 under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting the essential step that indicates that a substance that affects one or all of the characteristics listed in D(1)-D(9) of claim 1, as originally filed, indicates that it has an effect on Alzheimer's Disease.

Applicants respectfully traverse the rejection. However, in order to expedite the allowance of the present application, Applicants have submitted new claims (specifically new claims 95 and 213) containing language that provides a nexus between exposing the cells to a substance that has an effect on any or all of the characteristics listed in D(1)-D(9) of new claims 95 and 213 and having an effect on the recited characteristics of Alzheimer's Disease or related neurodegenerative disorders.

The last part of claim 95 reads, in pertinent part, "wherein said effect on said induction of any or all of said characteristics in D(1)-D(9) is indicative of the appearance or disappearance, respectively, of said characteristics of said Alzheimer's Disease or said related neurodegenerative disorders, wherein said related neurodegenerative disorder is one in which exposing said rodent brain cells to a cathepsin D-increasing agent or compound under conditions that increase the concentration or amount of cathepsin D in said cells to an effective concentration induces one or more of said characteristics of D(1)-D(9)."

Based on the new claims 95 and 213, Applicants respectfully request reconsideration and withdrawal of this rejection.

X. Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 1, 3, 4, 5, 6, 7, 8 and 9 under 35 U.S.C. § 102(a) as being anticipated by "Novel Cathepsin D Inhibitors Block the Formation of Hyperphosphorylated Tau Fragments in Hippocampus" by Bi *et al.* (hereinafter "Bi"). The Examiner contends that Bi teaches the treatment of hippocampal slices with lysosomal inhibitors to cause accumulation of amyloid precursor protein, phosphorylated tau and phosphorylated tau fragments. Additionally, the Examiner alleges that Bi teaches three novel cathepsin D inhibitors which block the hyperphosphorylation of tau fragments.

Applicants respectfully traverse the rejection. However, in order to expedite the allowance of the present application, Applicants respectfully submit the Declaration of Xiaoning Bi and Gary Lynch, in which Drs. Bi and Lynch state that the Bi reference is a publication of Applicants' own invention. Drs. Bi and Lynch state that they are the named inventors of the instant application and are co-authors on the Bi publication. Drs. Bi and Lynch state that Tasir S. Haque, A. Geoffrey Skillman, Christine E. Lee, Irwin D. Kuntz and Jonathan A. Ellman provided the inhibitors and chemical information related to the inhibitors used in the publication; Jun Zhou helped to prepare part of the slice cultures used in the study and provided other technical support; and Bin Lin provided physiologic verification of the cultures used in the study. Drs. Bi and Lynch state that Haque, Zhou, Skillman, Lin, Lee, Kuntz and Ellman did not contribute to the conception of the invention claimed in the captioned application.

Applicants respectfully submit that the Examiner should disqualify the Bi publication as prior art pursuant to MPEP § 715.01(c), which would moot the § 102(a) rejection.

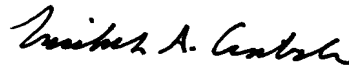
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Michele A. Cimbala
Attorney for Applicants
Registration No. 33,851

Date: Aug. 27, 2003

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600